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Review Article

Galectin inhibitors and nanoparticles as a novel therapeutic strategy for glioblastoma multiforme

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Abstract: Over the past two decades, the gold standard of glioblastoma multiforme (GBM) treatment is unchanged and adjunctive therapy has offered little to prolong both quality and quantity of life. To improve pharmacotherapy for GBM, galectins are being studied provided their positive correlation with the malignancy and disease severity. Despite the use of galectin inhibitors and literature displaying the ability of the lectin proteins to decrease tumor burden and decrease mortality within various malignancies, galectin inhibitors have not been studied for GBM therapy. Interestingly, anti-galectin siRNA delivered in nanoparticle capsules, assisting in blood brain barrier penetrance, is well studied for GBM, and has demonstrated a remarkable ability to attenuate both galectin and tumor count. Provided that the two therapies have an analogous anti-galectin effect, it is hypothesized that galectin inhibitors encapsuled within nanoparticles will likely have a similar anti-galectin effect in GBM cells and further correlate to a repressed tumor burden.

Keywords: Galectin-1, galectin inhibitors, nanoparticles, glioblastoma

Introduction

The year 2005 marks the discovery of temozolomide (TMZ) adjuvant therapy to prior surgical resection and adjuvant radiotherapy [1]. TMZ adjuvant therapy improved median survivability in a large cohort of patients from 12.1 months to 14.6 months in comparison to a group that solely received surgical resection and radiotherapy. In 2014, the large AVAglio clinical trial compares the use of angiogenic inhibitor bevacizumab with current standard therapy of care [2]. Adjuvant bevacizumab therapy was not found to increase survivability but did maintain a longer baseline quality of life and decreased the need for steroid therapy. Notably, addition of the therapy was associated with more severe adverse effects, supported by a separate clinical trial assessing the efficacy of bevacizumab in glioblastoma patients [2]. Despite the possibility of a promising new glioblastoma therapy, severe side effects and non-convincing efficacy resulted in the current standard of care remaining similar to nearly ten years prior to the study. Transitioning to the year 2019, the CeTeG/NOA-09 trial, a small phase 3 clinical study, found that dual therapy with TMZ and lomustine appears superior in select patients with good clinical correlates of prognosis, including a methylated O6-methylguanine-DNA methyltransferase (MGMT) promoter and a Karnofsky Peformance Score greater than 70% [3]; median overall survival was noted to be improved from 31.4 to 48.1 months. Given the introduction of these pharmacotherapies over almost two decades, median survivability in GBM patients as of 2023 is approximately 10-12 months [4] and research has struggled to identify novel efficacious pharmacotherapies for treatment. To aid in approaching glioblastoma management, GB a grade IV astrocytoma, has been recently split into two separate diagnoses depending on the expression of isocitrate dehydrogenase mutation (IDH status). IDH status, along with additional factors such as methylated MGMT promoter and Karnofsky Performance Score, are just a few critical factors that govern treatment approach, which is often limited to surgical resection, radiotherapy and TMZ therapy; use

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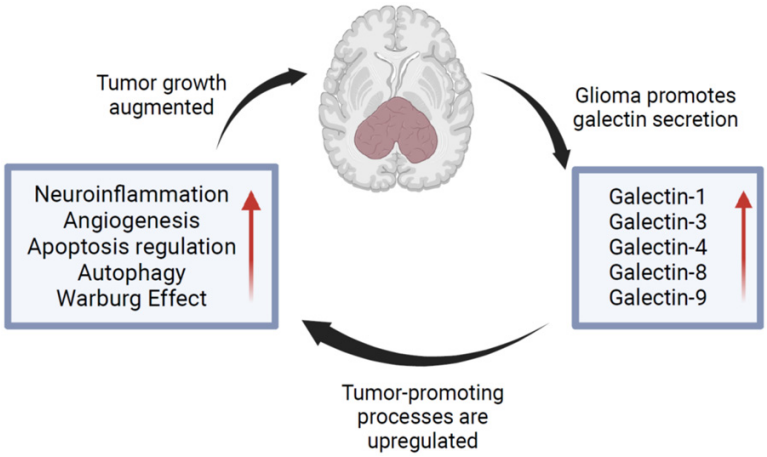

Figure 1. Depicts the cyclical nature of galectin-mediated tumor progression. Glioma cells upregulate various galectin isoforms found in the central nervous system. These glycan-binding proteins mediate various oncogenic processes including neuroinflammation, enhanced angiogenesis, apoptosis regulation, autophagy induction, and cancer metabolism. These processes increase glioma mass and metastatic potential which subsequently promotes a vicious tumor-promoting cycle.

of lomustine, bevacizumab, and other agents are utilized in unique circumstances.

Galectin role in neuroinflammation and neuro-oncology

Despite a lack of GBM pharmacotherapies producing clinical and prognostic benefit over decades, identification of anti-GBM molecular targets and clinical application with blood brain barrier penetrance vectors are showing promise in the field. Of particular interest, the galectin family of molecules is a protein of increasing focus in GBM treatment that is associated with pathological processes such as tumor proliferation and metastasis [5]. Galectins are carbohydrate-binding proteins classified under the family of lectins [6]. This family of proteins is capable of binding to complex carbohydrates through a conserved carbohydrate recognition domain (CRD) [7]. Within humans and other animal species, galectins have an intracellular and extracellular presence in various tissues with a relatively high incidence of morbidity and mortality, including the prostate, colon, pancreas, breast, and brain [7, 8]. Although there are approximately 16 galectins identified to date in humans and other animals [9, 10], galectin 1, 3, 4, 8, and 9 are particularly relevant to having functional effects on the nervous system malignancies and neuroinflammation. These various galectin isoforms share a common theme of promoting cancer growth through neuroinflammation modulation, angiogenesis, autophagy, apoptosis regulation, and regulating cancer metabolism [11]; a summary of this process is depicted in **Figure 1**. The following overview will serve to elucidate the individual roles of each galectin isoform in neuroinflammatory settings and highlight how each lectin contributes to a nervous system tumor microenvironment.

Galectin-1 (Gal-1)

Within the galectin family, Gal-1 is a member of the first group, of which there are three groups total [9, 10]. These divisions are primarily unique in the intricacy within their CRD and N-terminal domains, thereby impacting the glycoproteins they can interact with and the physiologic settings they can present in [9]. Gal-1 is a 14 kDa protein that has extracellular presence through cell-membrane interactions in addition to intracellular localization. Depending on the molecular characteristics of the galectins, these proteins can exert a tumor-promoting or tumor-suppressing environment [12]. The significance of Gal-1 in neurological tumor microenvironments can be related to its role in mediating inflammation and angiogenesis. Gal-1 is evidenced to have negative [13, 14] and positive neuroinflammatory effects [15] within the nervous system; depending on the cellular environment, Gal-1 can potentiate or attenuate neuroinflammation. Mice who encountered a knockdown of Gal-1 were identified to have reduced brain infiltrating myeloid cells and tumor-associated macrophages [16]. A pro-angiogenic effect is also encountered through analysis of *in vitro* murine gliomas cells with Gal-1 knockdown, demonstrating an elevation in chemokine ligand 2 (CCL2) and vascular endothelial growth factor (VEGF), both critical proteins in stimulating vascular growth. *In vivo* analysis of angiogenesis in murine models with Gal-1 knockdown further supports *in vitro* results, as these galectin deficient mice are noted to have reduced vascular density compared to wild-type mice with preserved Gal-1

activity. In opposition to this maladaptive role in inflammation, Gal-1 may have neuroprotective characteristics suggested by its activity in autoimmune processes [17]. In autoimmune disorders such as multiple sclerosis, mice with experimental demyelination treated with Gal-1 had a decrease in microglial activation with a subsequent shift toward an M2-polarized microglia and decreased astrocyte activation, corresponding to an anti-inflammatory effect [17]. Phenotypically, the mice treated with Gal-1 expressed less demyelination than their control counterparts, consistent with a reduction in disease severity. In addition to its protective effects in multiple sclerosis, Gal-1 reduces methamphetamine-induced neuroinflammation and strengthens the integrity of the blood-brain barrier. Evidence of neuroprotective effects is further displayed through the ability of Gal-1 to reduce seizure activity in mice with pilocarpine-induced seizures [18].

Within Gal-1's diverse role in immune regulation, there is a close interaction between natural killer (NK) cells and Gal-1 to promote tumor development [19, 20]. In healthy tissue environments, natural killer cells are able to destroy target cells undergoing early malignant transformation through an immune surveillance process [19]. Interestingly, glioma cells can evade NK-mediated immune surveillance through upregulating Gal-1 on their cell surface, giving them relative resistance to destruction; glioma cells that failed to express Gal-1 were able to destroy glioma cells. NK cells are proposed to lack glioma-destroying capabilities in Gal-1 expressing cells due to the presence of myeloid-derived suppressor cells (MDSCs). MDSCs are immature myeloid cells with a granulocytic or monocytic lineage that are formed during inflammatory states [21]. In healthy brain tissue, immature myeloid cells typically differentiate into microglia or dendritic cells, however in the setting of inflammation, these immatures myelocytes form into MDSCs that have a net tumor-promoting effect. In malignancies such as glioblastoma, the transformed cells upregulate Gal-1 to avoid immune surveillance and destruction; when Gal-1 is absent from these cells, NK-mediated destruction typically occurs. NK immune surveillance can be avoided in Gal-1 deficient glioma cells when MDSCs are depleted from the tumor microenvironment, yielding glioma growth [22]. This data suggests that Gal-1 expression on glioma cells may attenuate MDSC anti-tumor activity, allowing for immune surveillance and tumor progression. Aside from the lectin's role in inflammation, Gal-1 may aid the Warburg phenomena of glioblastoma tumor growth [23]. *In vitro* silencing of Gal-1 in glioblastoma tumor specimens is associated increased citric acid and alpha-ketoglutarate, suggesting a reversal of the Warburg effect toward oxidative phosphorylation.

Galectin-3 (Gal-3)

The third group of glycan binding lectins uniquely includes only Gal-3, a 25-35 kDa protein which possesses a carbohydrate binding domain in addition to a large N-terminal domain that assist in oligomerization to form pentamers [10, 24, 25]. Similar to Gal-1, this lectin withholds extracellular and intracellular activity but primarily localizes to the cytoplasm [26]. Depending on cellular location, Gal-3 can exert a variety of effects. Within the cytoplasm, Gal-3 interacts with proteins such as B-cell-lymphoma-2 (Bcl2), caspases, and metalloproteinase-7, to reduce apoptotic activity, mediate cell proliferation and metastasis, and exert a net tumor-promoting effect [27-29]. On the contrary, Gal-3 exhibits a tumor-regressing effect within the nucleus through enhancing Wnt transcription through direct-activity with Beta-catenin [30]. Similar to Gal-1, Gal-3 plays a critical role in mediating neuroinflammation, primarily through enhancing its response [31]. Neuroinflammation is demonstrated to be augmented in Gal-3 mice through interacting with toll-like receptors. Knockout of Gal-3 in mice with intranigral lipopolysaccharide-induced neuroinflammation was found to be associated with a reduction in proinflammatory markers and microglia; evidence of attenuated inflammation through the Gal-3 dependent toll-like receptor pathway is further supported in reducing mice neuroinflammation with hyperbaric oxygen treatment [32]. In addition to potentiating inflammation in animals, this group-3 lectin promotes neuro-angiogenesis and attenuates apoptosis [33]. Intraparenchymal injection of Gal-3 in mice is associated with increased cerebrovascular density, corresponding with an enhanced immunofluorescence of endothelial cells, as well as an increased number of blood vessels ranging in size. Galectin-3 injected

mice further demonstrated a reduction in the degeneration of apoptotic neurons. This attenuation of apoptosis corresponds with the stimulation of the phosphatidylinositol/AKT pathway, a critical pathway involved in cell-proliferation and apoptosis inhibition [33, 34]. These joint anti-inflammatory effects in combination with pro-angiogenic and anti-apoptotic properties of the group-3 lectin give it multiple characteristics that assist in tumor growth and proliferation. Gal-3 may also contribute to tumor growth through maintaining neuron proliferation in neuronal cells that are deprived of oxygen, simulating a Warburg-like effect that is characteristic of tumor growth in malignancies such as GBM [33, 35].

Galectin-4 (Gal-4)

Gal-4 is a member of the second group of glycan binding proteins, characterized by two distinct carbohydrate recognition domains at both the C and N-termini [10, 36]. This 17 kDa protein is primarily found in the gastrointestinal tract, although it is also prevalent within the genitourinary tract and central nervous system [37, 38]. Consistent with the prior mentioned lectins, Gal-4 is involved in oncogenesis, primarily through a pro-inflammatory, angiogenic, and anti-apoptotic effects [39, 40]. An increase in inflammatory cytokines G-CSF, IL-6, GRO alpha, and MCP-1, is apparent with intravenous injection of Gal-4 in murine models, corresponding with heightened tumor growth. Human CD14+ monocytes cultured with galectin-4 have reduced caspase-3 activity and decreased apoptosis, thereby promoting monocyte survival [40]. Gal-4 treated monocytes also demonstrate an inflammatory response with an associated increase in cytokines IL-6, IL-10, and TNF-alpha. Within the central nervous system, Gal-4 is hypothesized to be involved in myelin regulation, although its role is unclear and is skeptic within the community [41]. While there is evidence that the absence of Gal-4 does not impact the integrity and organization of oligodendrocytes, other studies suggest that Gal-4 may act as a negative regulator of oligodendrocyte synthesis [38]. Gal-4 displays a higher concentration at demyelinated axon segments, suggesting that an inverse relationship between the lectin and myelination may exist. Myelin has been found to avoid localizing to areas on an axon where galectin-4 is present, including the nodes of Ranvier [42]. This occurrence is currently being studied in autoimmune demyelinating disorders such as multiple sclerosis, where Gal-4 inhibition may express potential for pharmacotherapy.

Galectin-8 (Gal-8)

The second group of galectins additionally includes Gal-8, which also possesses two distinct carbohydrate recognition domains like Gal-4 [10]. This 43 kDa lectin is present in variety of physiologic tissues (e.g., prostate, colon, lung, brain) where it serves an extracellular function in angiogenesis and cell-adhesion, as well as an intracellular role in autophagy [43-46]. Angiogenesis regulation appears to be a major pro-inflammatory role of Gal-8 [44]. In the presence of lipopolysaccharide-induced inflammation, endothelial cells upregulate Gal-8 isoforms. Endothelial cells are further activated by Gal-8 and demonstrate platelet adhesion and upregulation of pro-inflammatory cytokines (e.g., GRO-α, GM-CSF, and IL-6) [47]. The mechanism by which Gal-8 stimulates angiogenesis may be explained through its interaction with endothelial ligands and vascular endothelial growth factor (VEGF) [48, 49]. CD166, termed activated leukocyte cell adhesion molecule, is a glycoprotein with angiogenic properties that has been determined to directly interact with Gal-8 [48]; addition of anti-CD166 antibodies subsequently decreased Gal-8 induced capillary formation. The interaction between Gal-8 and VEGF may further assist in explaining the role of the lectin in angiogenesis. Endothelial cells in the presence of Gal-8 and VEGF are noted in some instances to significantly enhance endothelial proliferation and migration [49]. Notably, there is ambiguity of the potential interaction between VEGF and Gal-8, given that there is evidence suggesting that the lectin can enhance angiogenesis in the absence of VEGF, contradicting studies that solely identify angiogenesis with both proteins present [48, 49].

Consistent with the role of Gal-8 in angiogenesis, the lectin's role in cell-adhesion likely assists in the development of malignancies. An increase of human colon cancer cell adhesion to endothelial cells is apparent with the presence of Gal-4 or Gal-8; this effect is terminated with the addition of lactose, thereby occupying the galectin binding sites [50]. This pro-oncogenic activity is further appreciated by observ-

ing the role of Gal-8 in breast cancer, where a knockout of Gal-8 or CD166 yields a reduction in tumor growth in a murine model of triple negative breast adenocarcinoma [51]. Gal-8 also plays a role in autophagy, which is a natural cellular recycling process that aids in cell survival and maintenance [52]. In the context of glioblastoma multiforme, Gal-8 may play a role in promoting glioblastoma cell autophagy, thereby augmenting cell growth [53]. The mechanism through which Gal-8 promotes autophagy may be elucidated in the setting of neurodegenerative disease [54]. Gal-8 assists in autophagy through detecting endomembrane damage and recruiting cargo receptor nuclear dot protein 52 (NDP52). Recruitment of NDP52 in turn initiates autophagy through the UNC51-like kinase-1 (ULK1) and TANK-binding kinase 1 (TBK1) complexes, resulting in the phosphorylation of downstream protein and receptors mediating autophagy [53, 55-57].

The role of Gal-8 in processes such as angiogenesis and cell-adhesion can further translate to the promotion of glioblastoma growth and metastasis [58]. *In vitro* glioblastoma cells display an augmentation of cell growth and migration in the presence of Gal-8; this effect is abrogated with the addition of lactose. Modifying glioblastoma tumor growth through enhancing tumor vasculature and cell-adhesion properties aids in explaining the tumor-promoting effect that the lectin has on various malignancies.

Galectin-9 (Gal-9)

The final member of the galectins with relevance to the central and peripheral nervous systems is Gal-9, a group-2 galectin that is approximately 34-39 kDa [10, 59]. Consistent with the other lectins, Gal-9 interacts in both intracellular and extracellular activities, with an emphasis of mediating innate and adaptive immunity [60]. One of the lectin's most well-studied molecular interactions involves the interplay between Gal-9 and its receptor Tim-3 to mediate various inflammatory pathways. T cell immunoglobulin and mucin-domain containing-3 (Tim-3) is an immune-checkpoint receptor that is found on T cells, dendritic cells, and macrophages [61]. High levels of Gal-9 present in tumor microenvironments activate Tim-3 receptors on T cells resulting in T-cell exhaustion in tumor-infiltrating leukocytes in humans and promoting tumor growth. Tumor growth is further regulated by the interactions of Gal-9 with Tim-3 on macrophages, as high Gal-9 levels can drive M2 macrophage polarization to enhance angiogenesis and support glioblastoma tumor growth [62]. Intriguingly, a contrasting effect between Gal-9 and Tim-3 is observed in the setting of diffuse pontine glioma, where anti-Tim-3 treatment in mice corresponds with elevated microglial activation and a pro-inflammatory state that promotes tumor growth [63]. Non-malignant nervous system pathologies such as intracerebral hemorrhage further support neuroinflammation inducing the polarization of microglia and supporting a pro-inflammatory environment [64].

Galectins in glioblastoma

In respect to glioblastoma, galectins have displayed carcinogenic activity primarily through immunosuppression, cell motility alteration, angiogenesis suppression, and apoptotic disruption [58, 65-67]. Analysis of Gal-1 knockdown in glioblastoma murine models has been correlated with a reduction in tumor myelocytes and microglia [16, 65]. Subsequent isolation of $CD8^+$ T cells in Gal-1 knockdown GBM mice demonstrated a weak but significant increase in interferon gamma production, suggesting that the lectin isotype has an immunosuppressive effect. These results are similarly noted in a study by Chen and colleagues who appreciated a reduction of M2 macrophages, myeloid derived suppressor cells, and inflammatory cytokines including monocyte chemoattractant protein-1, VEGFA, and TGF-beta [68]. Galectin suppression has also been shown to affect glioblastoma cell motility through the modulation of specific molecular targets. Integrins in particular have been observed to regulate various malignancies through cell adhesion and intracellular signaling [69]. Gal-1 knockdown in the setting of *in vitro* glioblastoma cells is correlated with decreased cell membrane integrin expression and an intracellular accumulation of integrin. The failure of integrin localization to the cell membrane suggests a reduced ability to assist in cell adhesion and facilitate intracellular signaling through cell membrane interaction. Glioblastoma cell migration and growth can further be affected by the silencing of a separate galectin isotype that is highly expressed in glioblastoma cells. Gal-8 has been shown to induce chemotactic migration of *in*

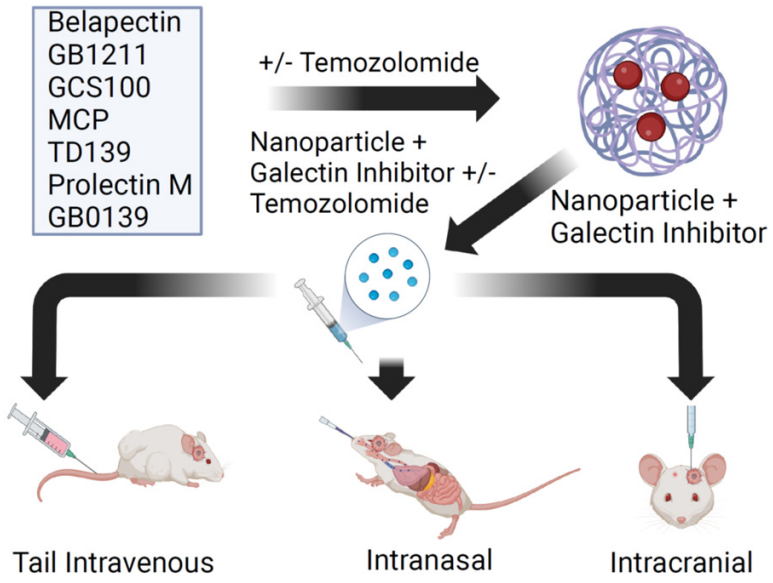

Figure 2. Begins by listing various galectin inhibitors tested in clinical trials for non-GBM pathologies. The listed galectin inhibitors, in addition to others not mentioned in the figure, can be added to a specific nanoparticle with or without TMZ. The galectin-inhibitor nanoparticle complex can then be prepared as a solution that can be administered to glioblastoma animal models, such as mice, through intravenous, intranasal, or intracranial routes.

vitro glioblastoma cells. GBM cell motility is intriguingly attenuated upon Gal-8 silencing with lactose, a well-known carbohydrate that inhibits galectin activity; similar results are observed with Gal-1 inhibition of GBM cells in an analogous study [66], which found the cells to lack lamellipodia in contrast to control cells.

The impairment of angiogenesis in glioblastoma also appears to be regulated partially by lectin proteins. GBM tumor infiltrated mice with Gal-1 inhibition by siRNA displays a decrease in angiogenesis [67]. Glioma-bearing mice stained with an endothelial cell marker further demonstrates a reduction of the marker in Gal-1 knockdown mice compared to wildtype models; vascular density was further significantly reduced [16]. Regarding the effects of galectin toward cell cycle regulation and apoptosis, Gal-8 silencing has been shown to result in a lower proportion of arrested glioblastoma cells and an increased proportion of GBM cells in a Sub-G1 phase, which represents fractional DNA that corresponds to apoptosis [58]. The prior mentioned literature on galectin's role in glioblastoma tumor development aids in elucidating the variety of methods by which anti-galectin therapy can negatively impact the glioblastoma tumor microenvironment.

Discovery of galectins and their application to tumorigenesis has promoted research devoted to anti-galectin therapy and carrier-based systems for clinical delivery. Galectin inhibitor molecules are shown to be efficacious as primary or assistant therapies across various carcinomas and sarcomas [70], as well as cardiovascular disease [71], pulmonary fibrosis [72], SARS-CoV2 infection [73], steatohepatitis [74], as well as autoimmune disorders such as psoriasis [75]. The use of galectin inhibitors across a spread of pathological processes not only showcases its therapeutic potential but further suggests the ability of the inhibitor to be applied to the treatment of a novel pathology, that shares similar characteristics to the aforementioned diseases. Integration of these galectin inhibitors with nanoparticle delivery systems appears both a viable and promising option for GBM therapy, considering galectin inhibitor treatment success with other malignancies and analogous GBM therapeutic success with anti-galectin siRNA therapy [76, 77]. As depicted in **Figure 2**, the galectin inhibitor and nanoparticle systems can be integrated into a pharmacotherapy that can be tested on animal models and optimistically human models to study the effects on glioblastoma tumor cells. The following review seeks to elucidate this theory of the possible therapeutic benefit of galectin inhibitors in glioblastoma treatment provided the advances in anti-galectin siRNA therapy and improvements in nanoparticle delivery systems.

Galectin inhibitors in pathological processes

Antagonists of galectin are being increasingly discovered for application toward varying pathologies. As of 2023, galectin inhibitors have been experimentally used for treatment of cardiovascular disease [78, 79], acute lymphoblastic leukemia [80], nonalcoholic steato-

Table 1. Displays clinically significant galectin inhibitors, associated pathologies, status of testing in clinical trials, adverse effects, and experimented routes of administration

Galectin Inhibitor	Relevant Pathology of Galectin Inhibitor	Phase I-IV Clinical Trial Tested (Y/N)	Elicited Adverse Effects	Studied Route(s) of Administration in Human Subjects
GR-MD-02 (belapectin)	Non-alcoholic steatohepatitis	Y	QT interval prolongation, headache, dizziness, nausea	Intravenous, Subcutaneous
GM-CT-01	Non-alcoholic steatohepatitis			Intravenous, Subcutaneous
GB1211	Healthy participants, Hepatic impairment	Y	Gastrointestinal (abdominal pain, diarrhea, constipation, dyspepsia), dry mouth, dry skin, skin rash, headache, dysuria, polyuria, menstruation disturbance	Oral
GCS100	Chronic lymphocytic leukemia, Prostate Adenocarcinoma	Y	Steroid-sensitive rash	Intravenous
PTX008	Acute lymphoblastic leukemia	N		N/A
Modified Citrus Pectin (MCP)	Cardiac and Renal Hypertrophy, Heart Failure, Prostate adenocarcinoma	Y	None elicited	Oral
N-Acetyl-D-Lactosamine (N-Lac)	Pulmonary Fibrosis	N		N/A
3,3-Bis-(4-aryltriazol-1yl) thiodigalactosides	Pulmonary Fibrosis	N		N/A
TD139	Idiopathic Pulmonary Fibrosis	Y	Taste disturbance, non-productive cough	Oral (inhaled)
Prolectin-M	SARS-CoV-2	Y	Taste disturbance, Shortness of Breath, Myalgia	Oral
GB0139	SARS-CoV-2	Y	QT interval prolongation with spontaneous resolution, nausea, sore throat, oral thrush, hair loss	Oral (inhaled)
C-3 aryl-substituted thiodigalactoside inhibitors	None	N/A	N/A	N/A
OTX008	Head and Neck Cancer Squamous Cell Carcinoma, Hepatocellular Carcinoma	N	N/A	N/A

hepatitis [81], breast and colon cancer [82], prostate cancer [83], pancreatic cancer [84], multiple myeloma [85], and interestingly SARS-CoV2 infection [86]. Galectin inhibitors also appear to possess the ability to increase sensitivity to existing chemotherapeutics when used as an adjunct therapy [87].

As of 2023, there are a multitude of galectin inhibitors that have been studied on specific pathological processes. Many of these galectin inhibitors specifically suppress Gal-3 activity, with some notable mentions including MCP [88], GR-MD-02 [75], GB1211 [89], and GCS100 [90]; these galectin inhibitors and many others listed in **Table 1** have been tested in clinical phase I/II trials or becoming therapeutic interests in the treatment of autoimmune disorders, non-alcoholic steatohepatitis, and various malignancies. Although these inhibitors have shown therapeutic efficacy across various pathological models in both animals and humans, these inhibitors have not yet gained popularity for glioblastoma pharmacotherapy or adjuvant therapy, despite it being shown that galectin promotes tumor growth in the disease [58, 66, 67, 91, 92]. Blood brain barrier permeability, a likely culprit of resistance to the use of aforementioned galectin inhibitors, has been appreciated as a predicament of delivering brain tumor therapy to patients [93, 94]. Fortunately, with the increasing development of nanoparticles showcasing effective BBB permeability [95, 96], drug-carrying capability [95, 97], and minimal adverse effects in animal models [95]; it appears that these inhibitors could be clinically significant in glioblastoma disease treatment. Before engaging in the study of galectins and galectin inhibitors on glioblastoma, a review of galectin inhibitors success in other disease processes will be discussed.

Galectin inhibitors in cardiovascular disease

Gal-3 and accompanying inhibitors are notably well-studied in atherosclerotic disease, heart failure, and other cardiac pathologies. Apolipoprotein E (ApoE), a major lipoprotein involved in triglyceride and cholesterol transport, was shown to be correlated with Gal-3 levels in aortic tissue when suppressed [98, 99]. Knockdown of ApoE in mice fed on high-fat diets demonstrated a significant upregulation of Gal-3 mRNA and protein levels [99]. Gal-3 mRNA and protein levels were also shown to be upregulated in unstable carotid endarterectomy (CEA) specimens when compared to stable CEA specimens. In addition to atherosclerosis, Gal-3 suppression has been correlated with clinical outcome in heart failure patients across numerous studies [78, 100-104]. Galectin inhibitor therapy was studied in aldosterone-salt treated rats with cardiac and renal hypertrophy [79]. Gal-3 inhibitor, modified citrus pectin (MCP), showed similar efficacy to spironolactone in reducing cardiac/renal hypertrophy and molecular markers of fibrosis. In a similar study, mice with hyperaldosteronism and isoproterenol-induced left-ventricular dysfunction, were studied to observe the outcome on aldosterone antagonist or Gal-3 inhibition on cardiac hypertrophy and fibrosis, as well as pro-fibrotic genes [105]. Isoproterenol-induced heart failure mice models showed a significant reduction in left ventricular fractional shortening, which was suppressed by both the aldosterone antagonist and MCP. Autopsy of the isoproterenol-treated mice also illustrated less cardiac hypertrophy with the use of the aldosterone antagonist or MCP. Notably, application of the aldosterone antagonist augmented with MCP provided a more significant reduction in cardiac hypertrophy and fibrosis. Of application, Gal-3 levels were notably increased in the heart failure mice models and subsequently reduced after use of the aldosterone antagonist, MCP, or both agents.

Galectin inhibitors in pulmonary fibrosis and Covid-19 respiratory infection

Gal-3 and its inhibitors have also demonstrated clinical utility across the study of fibrotic disease processes, specifically pulmonary fibrosis. Hypoxia-induced pulmonary hypertension rats were observed to have upregulation of Gal-3 that was sensitive to regulation by galectin inhibitors [106]. Inhibition of Gal-3 by N-Acetyl-D-Lactosamine (N-Lac), a Gal-3 inhibitor, noted reduced synthesis of collagen contributing to fibrosis, as well as reduction of pulmonary vascular remodeling and pulmonary artery pressure. Progression of pulmonary fibrosis was further reduced by the development of multi-targeting anti-galectin compounds, 3,3'-Bis-(4-aryltriazol-1-yl) thiodigalactosides. In bleomycin-induced pulmonary fibrosis mice, one intratracheal dose of the compound reduced anti-fibrotic activity. Interestingly, when comparing the compound to a gold standard anti-fibrotic medication, Pirfenidone, the compound demonstrated similar reduction in pulmonary collagen accumulation and fibrosis. A remarkable phase I/IIa study looked at the safety and pharmacodynamics of a gal-3 inhibitor, TD139, in treating a small sample of idiopathic pulmonary fibrosis (IPF) patients [107]. In this sample, 36 healthy and 24 IPF patients were randomized and given varying doses of inhaled TD139 or a negative control. The inhibitor displayed a half-life of approximately 8 hours and was overall well tolerated by participants. Notably, some adverse effects related to the drug were reported by the experimental group, with the majority experiencing mild taste distortion (dysgeusia). 11% of the group further reported acute onset cough; neither of these side effects appeared to have a dose-response relationship. Gal-3, as well as other pro-fibrotic biomarkers in the study, were noted to decrease in bronchoalveolar lavage samples, as expected post-inhibitor administration.

SARS-CoV-2 infection, known to induce pulmonary inflammation and damage, has also demonstrated clinical benefit from the use of galectin inhibitors [108]. SARS-CoV-2 spike proteins have been elucidated to share structural similarity to Gal-3 and facilitate entry of the virus into host cells [73]. This review proposed the idea of using Gal-3 antagonists given the structural similarity, which is remarkably studied to have benefits to clinical prognostication. Prolectin-M, a gal-3 antagonist, was studied for the treatment of SARS-CoV-2 infection (Galectin Antagonist Use in Mild Cases of SARS-CoV-2; pilot feasibility randomized, open label, controlled trial [109]). The study defines Covid-19 infectivity based upon the cycle threshold (CT), or the number of cycles needed to express fluorescence on RT-PCR, when looking at specific

viral genes. Administration of a chewable tablet of Prolectin-M increased cycle threshold of virally expressed genes significantly. Further testing by Sigmani and colleagues in a randomized, double-blinded, placebo controlled clinical trial in patients with mild-moderate Covid-19 infection correspondingly noted an increased in CT of viral genes in patients treated with Prolectin-M. Phase I and II clinical trials have also been conducted to explore pharmacodynamics and safety profile of the gal-3 inhibitor as an augmenting agent to gold standard Covid-19 pharmacotherapy. In a phase I/IIa randomized control trial termed, "Define", forty-one patients with Covid-19 pneumonitis were assessed upon adverse effects as well as galectin concentrations when given the gal-3 inhibitor, GB0139, when compared to standard treatment [86]. Across this sample, there was found to be no significant difference between the reported number of adverse effects experienced in both cohorts and decreased serum galectin levels were found in the experimental group. Notably, five patients did report adverse effects that were not experienced in the control group and thought to be possibly related to GB0139, including: QT interval prolongation with spontaneous resolution, nausea, sore throat, oral thrush, and hair loss. Patients who received GB0139 also had lower measured biomarkers significant for pulmonary fibrosis, consistent with prior literature. Regarding mortality rates, the study recorded seven deaths total with four deaths occurring amongst the experimental group; median duration of hospital stay was also 3 days longer. Despite this data, patients on the Gal-3 inhibitor had a significantly lower requirement for oxygen.

Galectin inhibitors in non-alcoholic steatohepatitis (NASH)

Gal-3 inhibitor therapy has shown some promise in the realm of treating non-alcoholic steatohepatitis with cirrhosis, given the fibrotic progression of the disease. The use of two galectin inhibitors, GM-CT-01 and GR-MD-02 (belapectin), were associated with improved histological analysis of liver specimens in mice with streptozotocin-induced non-alcoholic steatohepatitis and subsequent fibrosis [110]. Compared to control mice, the GM-CT-01 group was observed to have decreased fat deposition and inflammation, while the GR-MD-02 noted similar findings in addition decreased hepatocellular ballooning, and a subsequent significantly decreased non-alcoholic steatohepatitis score. Experimental groups of mice also demonstrated reduced collagen levels, correlating to fibrotic activity, in both inhibitor groups, with a marked decrease in the GR-MD-02 treated mice. A follow-up randomized phase I/IIa clinical study conducted by Harrison and colleagues further examined the safety and pharmacodynamic profile of the GR-MD-02 when applied to human participants [111]. Common adverse effects reported from the use of inhibitor included headache, dizziness, nausea, and QTc interval prolongation; a dose-response relationship with adverse effects was not appreciated. A reduction in fibrosis amongst the treatment group with the highest dose of the inhibitor, also provided significant reduction in fibrosis based upon blood tests looking at specific synthetized liver proteins such as haptoglobin and α-2 macroglobulin. A corresponding ultrasound used to assess liver stiffness, a correlator with fibrosis, also noted reduced liver stiffness in the GR-MD-02 treated patients. In opposition to this compelling data, a follow-up phase IIb study assessing the efficacy of GR-MD-02 on portal vein pressure and fibrosis did not find a significant effect on either measure; notably, a reduction in portal venous pressure and reduced incidence of varices were noted in a subgroup of non-alcoholic steatohepatitis patients without esophageal varices [112]. Galectin inhibitor GB1211 is further undergoing a clinical trial to determine the safety of the therapy in fifty-four participants with hepatic impairment [clinicaltrials.gov, indentifier: NCT05009680]. The study of the inhibitor in a separate phase I clinical study in healthy participants failed to identify serious or severe adverse effects across patients offered escalating dosages of the inhibitor [89]. Notably, treatment emergent adverse effects were found in both the single-ascending dose phase group and multiple-ascending dose phase group. In the single-ascending dose phase group, 14/56 patients were noted to have adverse effects, with eight of the patients being in the treatment group. Gastrointestinal side effects appeared to dominate the side effects in this group, including diarrhea, constipation, and dyspepsia. Integumentary disorders such as dry skin and rash were also elicited by three individuals. In the multiple-ascending dose

phase group, 8/22 patients elicited adverse effects, with seven of the patients being in the treatment group. Interestingly, similar gastrointestinal effects were found to predominate complaints amongst the patients, also including epigastric pain and abdominal distension. Adverse effects also pulled from other organ systems, including symptoms such as headache, dysuria, and polyuria. Of significance, across both groups, dose-response relationships were not appreciated with any of the elicited symptoms.

Galectin inhibitors in malignant processes

Discussion of galectin inhibitor therapeutic efficacy and safety in relation to diseases such as heart failure, Covid 19 infection, and steatohepatitis is important to note; however, application of these inhibitors in treatment of malignancies provides an additional connection toward understanding how these molecules may benefit glioblastoma patients. In the field of blood cancer research, studies have found the levels of galectin to be more significantly elevated in patients with treatment failure status post chemotherapy regimens [113, 114]. In a phase II clinical trial addressing both the safety profile and efficacy of GCS-100 for augmentation of treatment in chronic lymphocytic leukemia (CLL), GCS-100 was shown to have a relatively safe adverse effect profile and increase peripheral leukocyte apoptotic activity [115]. A quarter of the participants achieved primary remission with their appropriate chemotherapy regimen and adjunct GCS-100. Acute lymphoblastic leukemia (ALL) has also been shown to have increased expression of Gal-1 and benefit on the molecular level from anti-galectin therapy [116]. Acute lymphoblastic leukemia cells, when subject to the PTX008 Gal-1 inhibitor, have been found to agglutinate, a characteristic that is not typically present by the cell-line used; results were confirmed with flow cytometry. Exposure of ALL cells to PTX008 was also confirmed to interfere with adhesion and migration of cells, critical characteristics of tumor formation and metastasis.

Outside of leukemias, success with anti-galectin therapy has been appreciated in prostate adenocarcinoma. Modified citrus pectin treatment in animal models with metastatic lung lesions secondary to prostate cancer has been shown to significantly reduce lung lesions compared to control groups [83]. Use of both GCS-100 and MCP as an adjunct to cisplatin therapy in *in vitro* cells was shown to possibly enhance chemotherapy sensitivity through increasing apoptotic activity in a mechanistic fashion to cisplatin [117]. A phase II clinical trial assessing the therapeutic effect of MCP treatment on fifty-nine relapsed non-metastatic prostate cancer participants noted an overwhelming majority of the sample to have decreased or stable PSA over six months and absence of radiological disease progression [88]; the patients within the study were notably not on any radiological, surgical, or other medical therapy during the experimental protocol. Transitioning to hepatocellular carcinoma (HCC), Gal-1 inhibitors such as OTX008 have demonstrated efficacy in cancer treatment in murine models [118]. HCC is associated with elevated Gal-1 levels, which corresponds to poor prognosis and more aggressive tumor features [119]. *In vitro* HCC cells treated with OTX008 had decreased Gal-1 levels, which corresponded with reduced cell migration and invasion. In the setting of head and neck squamous cell carcinoma, OTX008 demonstrates similar results of tumor growth inhibition in addition to normalizing tumor growth vasculature [120]. Anti-galectin pharmacotherapeutic effects remain applicable across many other malignancies, including neuroblastoma, lung adenocarcinoma, melanoma, head and neck squamous cell carcinoma, pancreatic adenocarcinoma and ovarian cancer [84, 85, 121-124]. Despite the significant process of anti-galectin therapy in various malignant processes, galectin-inhibitors have yet to showcase in GBM animal models and humans.

siRNA anti-galectin therapy and nanoparticles in glioblastoma

Although anti-galectin agents have been poorly studied for treatment efficacy, anti-galectin siRNA therapy and galectin gene knockdown therapy has been moderately studied for potential therapeutic success. Part of the reluctance to these therapeutic options are likely related to the predicament of blood brain barrier penetrance that has limited glioblastoma treatment [96, 125]. Notably, there has been therapeutic advances in developing variations of nanoparticles containing chemotherapy agents, siRNA, and other anti-GBM agents that not only demonstrate adequate BBB pene-

Table 2. Lists the nanoparticle of interest, method of administration in animal models, and whether the nanoparticle has been tested with TMZ

Nanoparticle	Method of Delivery Tested in Animals	Tested with Temozolomide (Y/N)
Chitosan lipid nano capsules	Intracranial & Intranasal	Y
Exosomes	Intravenous	Y
Angiopep-2 nanoparticles	Intravenous	Y
Iron oxide nanoparticles	Intracranial, Intravenous	Y

trance [77, 126, 127] but also further reduce glioblastoma tumor burden in animal models [128]; use of these nanoparticles in combination with galectin inhibitors or siRNA will likely be more advantageous regarding treatment efficacy.

Chitosan-lipid nano capsules

Danhier and colleagues utilizes both ideas of anti-galectin therapy and nanoparticles by developing anti-Gal-1 and anti-EGFR siRNA-loaded chitosan-lipid nanocapsules [77]. The study demonstrates that intracranial administration of Gal-1 siRNA, EGFR siRNA, and TMZ through chitosan-lipid nanocapsules significantly improves survivability in mice from 34 to 39 days, suggesting a possible adjunctive therapy in patients with this brain tumor. These results show consistency with Messaoudi and colleague's *in vitro* analysis that demonstrates a significant increase in living GBM cells treated with anti-EGFR, anti-Gal-1, and TMZ combined therapy [129], suggesting that these agents may show promise as adjunctive treatments for reducing TMZ resistance. Provided that intracranial administration of pharmacotherapeutics are both invasive and non-efficient methods of delivery, an intranasal formulation of Gal-1 siRNA-loaded chitosan nanoparticles were developed [76]. In an *in vitro* assessment, the nanoparticles were subject to both murine and human GBM cell lines and were found to attach to both groups of cells. Additionally, cells exposed to the galectin siRNA nanoparticles demonstrated attenuation of galectin mRNA expression. Upon assessing BBB penetrance within mice, fluorescently labeled galectin siRNA was found to be present within nasal mucosa, olfactory bulb, and hindbrain. *In vivo* intranasal administration of the formulation also significantly decreased Gal-1 levels, representing both the efficacy of the nanoparticles to carry active siRNA and blood brain barrier penetration.

Combining previously studied galectin inhibitors with nanoparticles capable of effective BBB permeability may prove to be not only an effective treatment modality but also cost-effective when compared to siRNA treatments. A variety of nanoparticles exist in literature demonstrating adequate blood brain barrier penetrance and negligible elicited adverse effects in animal models. A summary of clinically relevant nanoparticles, method of administration, and exposure with TMZ is provided in **Table 2** for reference. Messaoudi and colleagues have multiple studies that support the safe use of chitosan-coated lipid nanoparticles with anti-GBM siRNA for glioblastoma pharmacotherapy [77, 127, 129, 130]. Titrating the concentration of chitosan has been shown to reduce the cytotoxic effect toward glioblastoma cells and likely other healthy glial cell types. Chitosan concentrations at 150 micrograms per milliliter were found to increase cell death of GBM cells, while concentrations with 100 micrograms were safe and non-confounding to experimental effect.

Exosome nanoparticles

Application of galectin suppression with corresponding tumor attenuation is demonstrated by the use of Gal-9 siRNA exosome-based nanoparticles in GBM infiltrated mice [128]. Mice infected with GBM and corresponding high tumor Gal-9 levels who were treated with Gal-9 siRNA loaded exosomes noted significant tumor volume decrease compared to the control. Analogous results can be noted in a separate study that appreciates increased survivability in mice with minipump infusion of both TMZ and galectin siRNA, when compared to either agent being used separately; increased survivability was correlated with decreased galectin levels [67]. Mice subject to the galectin siRNA were also notably found to have decreased levels of angiogenesis compared to their counterparts.

Regarding exosome-based drug carries, blood exosomes incorporated with metformin and phospholipase 2 (PLA2) have achieved BBB penetrance in mice and have been shown to modulate mitochondrial activity in glioblastoma cells, as well as increase survivability [131]. Metformin and PLA2-packed blood exosomes were observed to impair mitochondrial energy metabolism in GBM cells, associated with cell death. Intravenous administration of the packed blood exosomes in mice also achieved effective BBB penetrance and had an inhibitory effect of GBM progression. The efficacy of exosomes as drug carriers is further apparent through an observed induction of apoptosis and cell death in GBM mice injected intravenously with exosome-nanoparticles carrying doxorubicin [132].

Angiopep-2 nanoparticles

In addition to chitosan-lipid nanoparticles and exosome vectors, ligands such as angiopep-2 have been expressed on nanoparticles to increase permeability [126]. Angiopep-2 has a high affinity for receptor-related protein 1 (LRP1), which is a highly expressed receptor in the BBB. Conjugating angiopep-2 to lipid nanoparticles was found to have a 2.2-fold higher transport ratio than non-conjugated lipid nanoparticles and superior GBM cell uptake in comparison to non-conjugated particles. Angiopep-2 conjugated lipid nanoparticles carrying CRISPR-Cas9 also observes superior BBB penetrance and tumor penetrance with intravenous administration [133]. Employing angiopep-2-conjugated dendrimer nanoparticles for TMZ delivery has demonstrated considerable efficacy [134]. Dendrimers are hyperbranched nanosized macromolecules that are used for conjugating drugs and other ligands for delivery optimization. Utilizing dendrimers as a nanoparticle delivery system for TMZ and conjugating them with angiopep-2 for enhanced BBB permeability resulted in more than 90% inhibition of U87MG GBM cells compared to the 40% inhibition captured by TMZ use alone. Angiopep-2 nanoparticles have a dynamic use in GBM pharmacotherapy, as these nanoparticles can further be treatment modalities through photothermal therapy (PTT) and photodynamic therapy (PDT) [135]. PTT works to treat malignancies through utilizing strong light absorption by a photosensitizer to generate heat or reactive oxygen species (i.e. PDT). Lathanide-doped upconversion nanoparticles (UCNPs), which are capable of emitting near-infrared light for enhanced tumor penetration, can be conjugated with angiopep-2 to augment BBB permeability and deliver photothermal and photodynamic agents that effectively ablate GBM cells in mice and prolong survival. In contrast to infrared-light PDT, evidence of X-ray-induced PDT has also been shown to be efficacious in angiopep-2 bound nanoparticles carrying other chemotherapeutic agents (i.e. paclitaxel) [136]. X-ray-induced PDT with angiopep-2 bound nanoparticles carrying paclitaxel corresponded with significant growth reduction of GBM and prolonged survival time in mice.

Iron oxide nanoparticles

Iron Oxide Nanoparticles (IONPs) are a well-studied agent in biotechnology, with the ability to assist in various imaging processes and drug-delivery [137]. IONPs are a member of magnetic nanoparticles, consisting of an iron-oxide core and a chemically modified surface that may express dextran, lipids, or other small molecules that facilitate transportation [138]. There are three types of IONPs that vary in their chemical composition of iron, oxygen, and other metals; these formulations include magnetite (Fe_3O_4), maghemite (y-Fe_2O_3), and mixed ferrites (MFe_2O_4), where M can be substituted for nickel, zinc, cobalt, or manganese (30639256). Prior to delivery into a host, an internal magnetic field incorporated into the nanoparticle, or an external magnetic field can be utilized to assist in the physiologic localization of the particle. Chen and colleagues demonstrate the ability of an external magnetic field to assist in magnetic nanoparticles transport across the blood-brain barrier (BBB) [139]. The magnetic field alters BBB permeability through temporarily disrupting endothelial adherens junctions with nanoparticle assistance, thereby mediating the passage of the particle and circulating substances [140]. Evidence of this is depicted using iron oxide nanoparticles coated by gold and conjugated with polyethylene glycol that are subsequently administered through an intraperitoneal injection in mice [139]. The application of an external static magnetic field yielded an increase in the brain bioavailability of the particle compared to groups that did not utilize the magnetic field. The ability of IONPs to penetrate the BBB is further supported with the use of particles of different compositions

and delivery methods in drosophila and murine models [141-144].

In addition to displaying BBB penetrance, IONPs are biodegradable and sterilizable carrier molecules, giving them pharmacodynamic properties to carry out chemotherapeutic delivery [145]. The utilization of these nanoparticles to assist in chemotherapeutic delivery allows for nervous system-based malignancies to be treated with chemotherapeutics that may not possess inherent BBB permeability (i.e. TMZ). In the context of GBM, IONP carrier particles with anti-cancer agents have proved efficacious in *in vitro* BBB models. Polyethylene glycol conjugated-IONPs were utilized as carrier molecules for Salinomycin, an antibiotic displaying potential as an anti-cancer drug [146]. When the particles were cultured with the *in vitro* BBB GBM model, the particles had limited penetration and approximately 60% GBM cell viability. Subjecting the model to hyperosmotic disruption and assisting nanoparticle translocation with an external magnetic field significantly enhanced nanoparticle translocation across the BBB and reduced GBM cell viability to 38%. IONPs may further be used to deliver chemotherapeutics to GBM cells across the BBB in the absence of a magnetic field, through the use of BBB-permeable surface modifications [145]. Chemotherapeutic Gemcitabine was able to effectively penetrate the BBB in murine models with the assistance of IONPs conjugated with chlorotoxin, a BBB-permeable peptide. The nanoparticle-chemotherapeutic therapy also displayed similar *in vitro* GBM cell death comparable to Gemcitabine as a positive control. Similar results have been captured with using more standard chemotherapies for glioblastoma treatment (i.e. TMZ) in IONP formulations, displaying a significant increase in mice survivability when TMZ is given through an IONP formulation compared to TMZ alone [147]. Noting the possibility that the IONP nanoparticles could possess inherent cytotoxicity, current literature suggests that these nanoparticles do not alter cell viability [146, 148]. Similar to angiopep-2 conjugated nanoparticles, IONPs are also assisting in glioblastoma therapy through the use of PTT and PDT [148]. This method of therapy utilizes the generated heat after laser irradiation of photothermal agents to ablate tumor cells. The combination of PTT and PDT with iron oxide nanoparticles was capable of effectively killing *in vitro* glioma cells in the presence of laser irradiation.

Galectin inhibitors in clinical trials

As of date, two completed Phase 0 pre-clinical trials have been conducted on both primates and dogs with nervous system tumors to assess the safety and delivery of nanoparticles as possible therapeutic vectors [149, 150]. Intravenous administration of siRNA nanoparticles in primates has been demonstrated to be relatively safe [149]. Animals tolerated the therapy with zero mortality and the absence of grade 4 or 5 clinically related adverse events. Dermatologic manifestations of blue/purple discoloration of various body surfaces were appreciated notably in higher dosing groups; discoloration was also present on the surface of various organs throughout the body. Acutely, post-administration, animals were noted to have significantly decreased systolic and diastolic blood pressures which appears to resolve over a short period of time. Only two severe/grade 3 adverse effects of hypophosphatemia and lymphopenia were appreciated in subjects; both effects were found to decrease over the observed toxicology period. Importantly, the nanoparticles demonstrated BBB penetrance and tumor uptake, with unequal distribution throughout the brain tissue. The second preclinical trial involves utilizing polymeric magnetic nanoparticles (PMNPs) loaded with TMZ for possible therapy in dogs with MRI evidenced supratentorial tumors [150]. In seven out of the ten dogs who received with PMNPs, the nanoparticles effectively localized to the supratentorial mass; it is unclear by the authors if the three cases of failure to localize are the result of surgical error or therapeutic accuracy. The outcomes of these preclinical studies showcase the potential of nanoparticles to deliver agents relatively safely and efficaciously through intravenous or intracranial delivery. Additional phase 0 studies assessing the multitude of nanoparticles is necessary to further elucidate both safety and efficacy, as well as identifying superior nanoparticle delivery systems.

Challenges implementing galectin-inhibitors in the clinical environment

Despite the plethora of benefits that galectin-inhibitors offer for the treatment of disease and

malignancy, galectin-inhibitors possess some notable challenges to their implementation as pharmacotherapy. In therapeutic models, galectin inhibitors are limited in their ability to localize to a specific physiologic environment, their specificity and affinity for a particular galectin isoform, and through a lack of knowledge underlying the specific mechanisms by which these inhibitors attenuate disease state [151]. To date, there are no Gal-3 inhibitors that can penetrate the blood-brain barrier [152, 153]. Due to these molecule's polarization, they are dependent on pharmacotherapeutic vectors to localize to central nervous system. Gal-3 inhibitors also lack specificity and affinity toward Gal-3 [154]. Although Gal-3 is unique in its possession of a large N-terminal domain compared to other galectins, this lack of specificity and affinity toward Gal-3 can likely be explained by the similarities in the carbohydrate recognition domain. Gal-3 inhibitors have been discovered to interact with other galectin isoforms, potentially disrupting the normal physiologic functions of other lectins and confounding data collection [155]. The development of high affinity and high selectivity galectin inhibitors, such as aminopyrimidine-galactose hybrids, are necessary as they can yield a significantly higher selectivity for Gal-3 compared to Gal-1. Unfortunately, aminopyridines and other galectin inhibitors such as PTX008, Bruceine A, GB1490, and others are poorly studied in their mechanism of inhibition and clinical application [151, 155-157]. Regarding mechanism of inhibition, although galectin-inhibitors have been noted to attenuate inflammatory processes and tumor-promoting effects through interacting with the carbohydrate recognition domain and N-terminal domain, the specific mechanism of attenuation is unclear [73]. This deficit is largely attributed to a lack of knowledge regarding the specific physiologic pathways that are altered by galectins and their role in regulating these pathways [158]. Although more research into the physiologic mechanisms of galectins, galectin-inhibitor pharmacodynamics, and clinical application are needed before considering these proteins as therapeutic modalities, a great deal of potential exists for the drugs to be applied to clinical environments in various pathological processes.

Conclusion

Considering the available literature, galectin inhibitor therapy through nanoparticle delivery systems appears to be a viable pharmacotherapy for glioblastoma. Galectin inhibitors show safety and positive prognostication across various non-glioma malignancies. Evidence of glioma tumor regression and safety with analogous galectin inhibitors, anti-galectin siRNA, and development of nanoparticle delivery systems supports the consideration of well-studied inhibitors such as belapectin, modified citrus pectin, and others to be experimentally tested. Notably, there are challenges toward the clinical implementation of galectin-inhibitors, including considerations such as isoform affinity and specificity, inhibitor localization to a specific tissue, and a deficiency in the knowledge of galectins and molecular inhibitors. An additional consideration of therapeutic efficacy includes the variety of nanoparticle formulations including lipid nanoparticles, exosomes, and metal-based nanoparticles and discovering a superior nanoparticle delivery system to compliment a galectin inhibitor [159, 160]. Initiation of these tests can address the *in vitro* effects of nanoparticle-based galectin inhibitors on glioblastoma cells and progress to analysis in murine and other animal models, with the goal of initiating Phase I and II clinical trials in human subjects using a galectin inhibitor-based nanoparticle for treatment of GBM.

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Disclosure of conflict of interest

None.

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